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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/526,298	03/15/00	EVANS R	P41-9321

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HM22/0822

EXAMINER	
MCGARRY, S	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 08/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/526,298	Applicant(s) EVANS ET AL.	
	Examiner Sean McGarry	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-19 and 35-53* is/are pending in the application.

4a) Of the above claim(s) *49-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19 and 35-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's affirmation of the provisional election of Group I in Paper No.7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 49-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 7.

3. Claims 14-19 and 35-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a methods drawn to the induction or repression of a specific gene by a member of the steroid/thyroid superfamily of receptors which associates with at least the dimerization domain of ultraspiracle receptor, in the presence of ligand for said member, where the expression of said gene is maintained under the control of a hormone response element to which said member binds where the method comprises exposing the expression system to at least the dimerization domain of an ultraspiracle receptor where the method is in vitro or in cells in culture, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with

these claims drawn to nucleic acid based therapy. This rejection is maintained for the same reasons set forth in the Official Action mailed 10/20/00.

Claims 14-19 and 35-48 are drawn to nucleic acid based therapies.

The instant claims are drawn to nucleic acid therapy and involve methods of introducing and expressing exogenous genes and nucleic acid sequences in specific cells in a whole animal. For example, the claims require the integration of a gene coding for an ultraspiracle receptor and/or the introduction of a construct containing the hormone response sequence where said construct would further comprise a desired exogenous gene to be regulated by the ultraspiracle receptor (see pages 10, 21, and 22 of the instant specification, for example).

The art of gene therapy is an unpredictable art that requires much guidance. The instant specification provide guidance for the instant methods in cells in culture but does not provide guidance or example that would show by correlation the instant methods as the are drawn to nucleic acid based therapies. For example the instant specification fails to teach one of skill in the art how to integrate the gene construct for the exogenous ultraspiracle receptor to specific desired cells such that expression would be at a level adequate for inducing the expression of a gene under the appropriate hormone repone element. The targeting of specific cells would be required, for example in cases where as applicant contemplates and claims, a method of selectively killing cells and for directing expression of a desired gene in a specific cell type or tissue type. The instant specification fails to provide adequate guidance for one of skill in the art to create a "pre-existing system in an animal" and apply the instant methods. The establishment of such a system requires

the introduction of an exogenous nucleic acid construct into cells of an animal and also to provide at least the dimerization domain of an ultraspiracle receptor where the exposure is disclosed in the specification to embrace exposing these cell at least the dimerization domain of an ultraspiracle receptor per se and also a DNA that encodes at least the dimerization domain of an ultraspiracle receptor.

The instant specification provides only scant and general guidance for introduction of genes to a whole animal and provide no specific guidance. Nucleic acid based therapy is an unpredictable art and one of skill in the art is in need of specific guidance for any specif gene therapy. The art has shown that there are no routine methods and has further shown that one cannot expect positive results using methods known today yet at the time of the instant invention. Ronald Crystal states [Science Vol. 270:404-410, 1995] at page 409 "[a]ll of the human transfer studies have been plagued by inconsistent results, the bases of which are unknown." Crystal reviews the state of the art of gene therapy and discusses the obstacles that still remain to effect nucleic acid based therapies and discusses the potential of nucleic acid based therapies. Verma et al [Nature Vol. 389:239-242, 1997] discusses the problems of gene therapy artisan face even today. It is stated "[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." and further "[t]he choice of tissue in which to express the therapeutic protein will ultimately depend on considerations such as the efficiency of gene delivery, protein modifications, immunological status, accessibility and economics." and also"[t]he Achilles heel of gene therapy is

gene delivery, and this is the aspect . . ." It is clear, that although gene therapy provides promise for the treatment of disease and applicants invention to would be promising in a gene therapy, there are general obstacles faced by the artisan in the practice of gene therapy where the instant specification fails to provide adequate guidance to overcome these obstacles to practice the instant invention. This position is further taken in view of the disclosure of Orkin et al where it is also discussed the many problems of gene therapy that need to be overcome (see numbered pages 1, 3-14 and 30-35). It is clear from the art that the art of gene therapy is unpredictable and the state of the art at the time of invention would require specific guidance for any particular gene therapy where no routine methods are known. One of skill in the art would need to overcome the basic problems addressed in the art to practice the instant invention as it relates to gene therapy.

4. Applicant's arguments filed 4/23/01 have been fully considered but they are not persuasive.

Applicant argues that the examiner has taken to narrow a view of the claimed invention. It is unclear how the interpretation is to narrow. The claims are drawn to nucleic acid manipulation (e.g. introduction and modulation of expression) in a subject. The first paragraph of the rejection of record indicates that subject matter which is enabled and the body of the rejection discusses that scope of the claimed invention that is not enabled. If a portion of a claimed method is not enabled, the claim per se is not enabled. The utility for modulating nucleic acids in a subject clearly embraces gene therapy. Applicant also asserts that the claims do not require the delivery of

DNA constructs into cells while the cells are in a subject and argues that this could be done ex vivo. The claims do embrace the delivery of DNA into cell that are in an animal and further the instant specification provides one sentence for the ex vivo methodology argued. What cell types would one use in ex vivo applications, how would one make them such that ligands delivered in vivo would enter the ex vivo delivered cells such that a modulation could be established, for example? Applicant also argues that since it has been shown that nucleic acids have been delivered to subjects in vivo the instant claims are enabled and the art is not unpredictable. However the claims do not require only that a nucleic acid construct be delivered to a cell in an animal, for example, but requires that this construct enable the modulation of a specific target nucleic acid.

5. Claim 17 **was** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection has been withdrawn in view of applicants amendments filed 4/23/01.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. Papers should be faxed to Art Unit 1635 via the PTO Technology Center Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1635 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 22, 2001

SEAN McGARRY
PRIMARY EXAMINER
Technology Center 1600